Review Article

Potential pleiotropic beneficial effects of adjuvant melatonergic treatment in posttraumatic stress disorder

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Abstract

Loss of circadian rhythmicity fundamentally affects the neuroendocrine, immune and autonomic system, similar to chronic stress and may play a central role in the development of stress-related disorders. Recent articles have focused on the role of sleep and circadian disruption in the pathophysiology of posttraumatic stress disorder (PTSD), suggesting that chronodisruption plays a causal role in PTSD development. Direct and indirect human and animal PTSD research suggests circadian-system-linked neuroendocrine, immune, metabolic and autonomic dysregulation, linking circadian misalignment to PTSD pathophysiology. Recent experimental findings also support a specific role of the fundamental synchronizing pineal hormone melatonin in mechanisms of sleep, cognition and memory, metabolism, pain, neuroimmunomodulation, stress endocrinology and physiology, circadian gene expression, oxidative stress and epigenetics, all processes affected in PTSD. In the current paper, we review available literature underpinning a potentially beneficiary role of an add-on melatonergic treatment in PTSD pathophysiology and PTSD-related symptoms. The literature is presented as a narrative review, providing an overview on the most important and clinically relevant publications. We conclude that adjuvant melatonergic treatment could provide a potentially promising treatment strategy in the management of PTSD and especially PTSD-related syndromes and comorbidities. Rigorous pre-clinical and clinical studies are needed to validate this hypothesis.

Introduction

The specific aim of this article is to review the available literature on a potentially beneficiary role of an adjuvant melatonergic treatment in PTSD, through restoring sleep and circadian alignment at different pathophysiological and molecular levels. For this scope, common neurobiological underpinnings of PTSD and circadian misalignment are outlined and human and animal research findings on melatonergic effects on different levels of the common pathophysiology are presented as a narrative review, providing an overview on the most important and clinically relevant publications.

The human circadian system and melatonin

The human circadian system (CS) creates and maintains cellular and systemic rhythmicity, through temporal organization and coordination of many physiological and transcriptional processes in the organism [1, 2]. The human central CS includes the intrinsically photosensitive retinal ganglion cells (ipRGC), the retinohypothalamic tract, the suprachiasmatic nucleus (SCN), the superior cervical ganglia and the pineal gland (PGL) [2, 3]. The SCN is the primary pacemaker of the central CS, coordinating sleep and other physiological functions such as immune and autonomic activity, metabolism, neuroendocrine hormone secretion and thermoregulation via neuronal and humoral signals [1, 2, 4, 5]. Sleep homeostasis acts synergistically and bidirectionally with the central circadian system, but also independently restorative towards optimization of the internal temporal order [6]. Thereby, sleep onset and sleep stage timing are in particular associated with circadian gene expression in the SCN and thus tightly ruled by the CS [7]. Additionally, a peripheral oscillating network of partly independent orthologs and paralogs of the core CS components (peripheral *Zeitgebers*) orchestrates biological functions from the level of genetic variance and ubiquitously circadian gene expression to peripheral circadian oscillations [8-10]. The high complexity of this multi-oscillator system and the high number of external and internal rhythmicity-modulating factors enables numerous possibilities for interactions with different tissue-specific importance [10].

The major effector of the central CS is the PGL and its neurohormone melatonin [11]. Melatonin displays robust and predictable secretion rhythms, that synchronize numerous physiological processes in photoperiodic species [12, 13]. The time course of melatonin secretion from the pineal gland is strictly adapted to the circadian rhythm and controlled by the SCN through GABA-ergic inhibition reactive to a restricted bandwidth of visible light (460-480 nm, i.e. blue light) [12, 14]. Short-wavelength visible light in the blue-appearing portion of the spectrum is most potent for melatonin regulation than other action monochromatic light spectra [15]. The major route of melatonin delivery is the direct release into the cerebrospinal fluid (CSF) of the third ventricle assisted by a number of epithalamic structures (e.g., interpinealocyte canaliculi, evaginations of the posterodorsal third ventricle) [16]. Melatonin concentration reaches high levels at night and low levels during the day, with peak plasma levels between 0200 h and 0400 h, thus coinciding with decreases in core body temperature, alertness and performance [12, 13]. Melatonin exerts many peripheral physiological actions on cell-specific control by binding to the G-protein-coupled melatonin membrane receptors MT_1 and MT_2. Furthermore, melatonin may interact with cytoplasmic factors (i.e. quinone-reductase-II/MT_3 receptors, calmodulin) and nuclear receptors (i.e. retinoid acid receptor related orphan and Z receptors (ROR, RZR). Via these interactions, melatonin modulates peripheral oscillators and connected secondary molecular pathways, while numerous other actions of melatonin are receptor independent (e.g., radical scavenging – see also below) [10, 17-21] (*cf*. Figure 1). The sharp elevation of nocturnal CSF melatonin levels could also have substantial protective utility and be responsible for the sleep-specific tissue recovery after the daily free radical brain damage due to high oxygen utilization [16]. CSF melatonin protects the whole brain as it circulates through the aqueduct into the subarachnoid space surrounding the brain and penetrating into the deepest portions of the neural tissue where it diffuses into the neural parenchyma [16].

On the other hand, melatonin directly influences, in turn, SCN activity and central circadian “clock” mechanisms. Thereby, melatonin acts as a modulator of the electrical activity in SCN neurons through MT_1/MT_2 [22, 23]. In addition, melatonin interacts with the

"clock" gene (Per1, Per2, Cry1, Cry2, clock, Bmal1, etc.) proteasome transcription loops in the SCN, thus modulating circadian rhythms and adjustment to environmental photoperiod changes [24]. These extremely multifaceted chronobiotic regulatory actions (see also below) have led to the recognition of melatonin as the most important natural substance modulating sleep and circadian rhythm [11-13, 17] and as one of the most pleiotropic biological signals in photoperiodic species [17, 25].

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Chronodisruption and stress

This integrative system of complicated circadian hierarchy enables the interaction of circadian, hormonal, and metabolic systems towards an optimal homeodynamic state, physical health and environmental adaptation. In the last years, accumulating evidence outlines the importance of the human CS, melatonin and circadian-related factors in the maintenance of health. A critical loss of this time order at different organizational levels is defined as chronodisruption and introduces a breakdown of harmonious functioning internal biological systems and appropriate biobehavioral adaptation to external stimuli [26] with short and long-term molecular, pathophysiological and epigenetic impact [27]. Dysfunction of endogenous clocks, melatonin secretion and melatonergic signalling could, for example, contribute to altered gene expression and herewith to numerous physical and mental disorders [10].

Apart from inadequate exposure to the light-dark cycle (i.e. reduced exposure to sunlight during day, increased light exposure at night, natural light isolation), further both external and internal factors may also lead to a gradual shift or a total desynchronization of the CS. For example, acute and chronic physical, psychological, inflammatory and metabolic stress can affect the CS [28-32]. On the other hand, chronic circadian disruption may gradually change the fundamental properties of brain systems regulating neuroendocrine, immune and autonomic stress systems, similar to chronic stress [4]. Chronodisruption may,

thus, sensitize individuals to stress and increase vulnerability for stress-related disorders [33, 34].

Chronodisruption in posttraumatic stress disorder

Posttraumatic stress disorder (PTSD) in DSM-V is classified as a trauma- and stress-related disorder with distinctive symptoms following a psychologically distressing event outside the range of usual human experience [35]. The estimated lifetime prevalence of PTSD in the general U.S. population lies between 5-6% in men and 10-14% in women [36]. Diagnostic criteria include current symptoms from each of four symptom clusters: intrusion, avoidance, negative alterations in cognitions and mood and alterations in arousal and reactivity including sleep disturbances. Sleep disturbances, especially, are prominent clinical features of PTSD, while there is evidence that sleep disruption after trauma may represent a core, rather than a secondary feature of PTSD and, thus, mediate the neurobiological correlates of the disorder through impaired homeostatic balance [37-40]. PTSD is characterized by a vast number of symptoms, co-morbid medical conditions and biological findings, also related to sleep deprivation (SD) and circadian disruption, suggesting that chronodisruption may represent a potential common underlying neurobiological link. Recent articles have focused on the role of chronodisruption in the pathophysiology of PTSD, suggesting that sleep and circadian dysregulation play a causal pathophysiological role in PTSD development [39-41] (*cf*. Figure 2). For example, disrupted melatonin levels in the first 48h after traumatic stress exposure were shown to be associated with a higher risk of PTSD development [42].

In this context, sleep and circadian regulation through exogenous circadian entrainment (e.g. melatonergic treatment) could play a central role in the prevention and treatment of PTSD. Nevertheless, relevant clinical literature is relatively sparse and mostly indirect. To date, the evidence-based recommendation for the first-line pharmacological treatment of PTSD includes only selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) [43].

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Melatonergic effects on PTSD-specific pathophysiological states and symptoms

Sleep

Stress is known to influence sleep physiology and dream patterns. Acute and chronic stress exposure may cause both immediate and long-lasting sleep disruption [38, 44, 45] which may, in turn, enhance maladaptive stress regulation [46]. Sleep disturbances are prominent clinical features of PTSD [37, 39], often resistant to first-line treatments [47-49] and closely related to higher PTSD psychopathology [50, 51], while their effective treatment is associated with significant improvement of overall PTSD psychopathology [52-54]. Sleep disturbances in PTSD are associated with sleep-related arousal regulation and other functions (i.e. dreaming, memory consolidation) [55] and include hyperarousal states, sleep avoidance and insomnia, nightmares, sleep terrors and nocturnal anxiety attacks, body-movement and breathing-related sleep disorders [37, 40, 56-58]. Most polysomnographic studies demonstrated heightened sympathovagal tone during rapid-eye-movement (REM) sleep using heart rate variability measures, as well as particularly fragmented REM sleep pattern and reduced REM theta activity in early-stage and sustained PTSD [39, 46, 55, 57-61]. On the other hand, REM sleep disruption in the immediate aftermath of a trauma has been associated with increased REM-related sympathetic activation, representing a major moderating and predictive factor in the development of PTSD [40, 62, 63]. Interestingly, there is also evidence that sleep impairment prior to traumatic stress exposure could contribute to PTSD vulnerability and development [64, 65]. These two studies both showed that reporting sleep complaints at baseline resulted in a 2.5-fold increased risk of fulfilling PTSD criteria 3 months after a trauma in general population admitted to a hospital or after deployment in active military troops respectively.

Sleep propensity and sleep rhythm regulation are temporally related to the SCN-controlled nocturnal rise in melatonin, which, in turn, exerts its hypnagogic and entraining action through MT_1 and MT_2 receptors of the SCN [23, 66, 67]. The different sleep stages are

also strongly circadian-bound and modulated by melatonin [68-70], thus suggesting that melatonergic effects may be beneficial for ameliorating sleep disruption and related disturbances. Numerous randomized-controlled trials (RCTs) and meta-analytic studies have repeatedly confirmed efficacy of exogenous melatonergic treatment. Melatonin and melatonergic agonists, when time-appropriately administered, are associated with significantly reduced sleep onset latency and increased sleep propensity, efficiency, quality and total sleep duration in patients with SD, such as insomnia [23, 67, 68, 71-75]. In addition, melatonergic treatment has been shown to lead to i) increased REM sleep percentage and continuity, normalization of sleep patterns and improvements in subjective measures of daytime dysfunction in neuropsychiatric patients with reduced REM sleep percentage or altered sleep patterns, ii) increased REM sleep percentage, advanced sleep/wake rhythm phase adjustment and sleep and wake-up propensity in healthy adults, as well as to iii) partial prevention of experimentally-induced REM suppression with pindolol in rats [67, 68, 70, 76]. Melatonergic treatment also shows a benign side-effect profile and safety in the short- and long-term administration, with no wearing-off in efficacy and without any withdrawal effects or dependence risk [23, 71, 74, 75, 77]. In addition, it has been proven also effective in the treatment of primary insomnia, circadian rhythm-related sleep-wake disorders, REM sleep behaviour disorders, body-movement and breathing-related sleep disorders, as well as in sleep disturbances within the scope of various psychiatric disorders (e.g., schizophrenia, depression) [72, 75, 76, 78-81]. Thus, melatonergic treatment could be an appropriate alternative for handling PTSD-specific sleep-related symptoms, while its implementation could even find use in PTSD prevention.

Circadian gene expression

Molecularly, the biological clock is based on the transcriptional/translational feedback loop of clock genes, not limited to the SCN, but depending on its neuroendocrine/neuronal output [82]. Animal research provides evidence that circadian-related genes play a role in the neurobiological response to stress, while chronodisruption can lead to alterations in the

physiological oscillations of circadian-related gene expression in humans [83-86]. Animal research on PTSD and chronic mild stress models provides evidence that stress disrupts the regulated gene expression of circadian-related genes (e.g., Per 1, Per 2, Clock, Cry 1, Bmal 1, Npas 2) in several tissues including the hippocampus and the SCN [87-89]. Recently, a genome-wide association study showed that the retinoid-related orphan receptor alpha (RORA) gene, a clock gene, may represent a risk gene for PTSD [90].

Melatonergic regulation is known to adjust and reset amplitude and phase of CNS (e.g., SCN, hippocampus, pituitary pars tuberalis) and peripheral (e.g., adrenal gland) circadian-related gene transcriptional oscillation independently of previous phase [91-95]. In addition, immediate melatonergic treatment directly after exposure to predator scent stress, normalized the altered expression of Per 1 and Per 2 genes in hippocampal regions of rats, thus suggesting a possible immediate protective effect [88]. In addition, animal studies demonstrate a melatonergic regulation of peripheral clock genes oscillation in the adrenal gland and their responses to ACTH [91, 92, 96-98]. Melatonin is especially considered to play a partially moderating role in the circadian regulation of GR function (e.g. acetylation of GR, GR transcriptional activity, GC sensitivity, cell proliferation, etc.) [99-103], which is crucially involved in PTSD pathophysiology (see below).

Hypothalamic-pituitary-adrenal-axis and glucocorticoid signaling

Hypothalamic-pituitary-adrenal (HPA) axis activity is closely linked to the CS and characterized by circadian rhythmicity [99, 104-106]. Through various pathways, the SCN and melatonin synchronize hypothalamic neuroendocrine neurons, influence adrenal sensitivity to adrenocorticotropic hormone (ACTH), stimulate circadian glucocorticoid (GC) hormone secretion and interact with the own peripheral rhythm of the adrenal gland [99, 102, 107, 108]. Furthermore, cortisol and corticotropin-releasing hormone (CRH) are suggested to directly modulate PGL activity [29, 109, 110]. Interestingly, the phase angle between cortisol and melatonin onset has been identified as a potential useful biomarker in human stress-related research for distinguishing between healthy and depressed individuals [111].

Neuroendocrine findings in PTSD reveal increased central CRH levels, altered HPA axis reactivity with enhanced negative feedback inhibition and blunted circadian cortisol rhythm and cortisol awakening response (CAR), while some studies - but not all - have shown decreased circulating concentrations of cortisol [112-121]. An enhanced HPA axis negative-feedback sensitivity in PTSD is in line with an increased GC sensitivity and altered GC receptor (GR) responsiveness and density in different cell types in these patients [122-126]. Similar changes in HPA axis activity (e.g. reduced ACTH levels, increased CRH levels, increased/decreased cortisol levels) with altered endocrine reactivity to stressors (e.g., attenuated pituitary ACTH response, increased adrenocortical ACTH sensitivity) and blunted circadian cortisol rhythm and CAR have been also reported in patients with chronic insomnia, as well as in human and animal SD studies [33, 127-132], while pharmacological GR-antagonism has been found associated with insomnia symptoms improvement [133]. These similarities suggest that the HPA axis- and GC-signaling-specific alterations in PTSD may be partially mediated by sleep and circadian disruption [39, 134, 135].

Melatonin has been also shown to directly inhibit the adrenocorticotropin-stimulated cortisol production in the primate and human adrenal gland [97, 98]. In animal studies, chronic exogenous melatonergic treatment counteracts synthetic GC-induced dysregulation of the HPA axis. Melatonin has been shown to decrease hypothalamic CRH levels, to prevent the chronic stress-induced ACTH decline and to attenuate the adrenocortical secretory response in acute and chronic stress models [136-139].

Sympathoadrenal and autonomic nervous system

The physiological fluctuations in circadian autonomic activity seen in humans are mainly modulated by the CS rhythms, through projections to pre-autonomic hypothalamic neurons responsible for cardiovascular autonomic control [140-142]. Chronodisruption is associated with increased sympathoadrenal activity and blunted autonomic and cardiovascular rhythmicity and responsiveness, constituting a major cardiovascular risk factor [33, 143]. PTSD patients exhibit similar autonomic findings such as hyperarousal, exaggerated startle

responses, increased basal heart rate and sympathovagal balance during day and night, increased autonomic responses to traumatic stimuli and norepinephrine levels, blunted autonomic diurnal rhythmicity and salivary alpha-amylase awakening response and overall reduced heart rate variability [63, 120, 144-150]. These findings suggest that chronodisruption-related chronic neuroautonomic dysregulation, could be responsible for the higher cardiovascular risk seen in this disorder. In particular, PTSD has been repeatedly associated with hypertension, cardiovascular diseases and myocardial infarctions and is increasingly considered an established risk factor for cardiovascular disease [151-156].

Melatonin has gradually gained interest as a potential cardioprotective and antihypertensive agent [157-159]. Apart from its antioxidant and scavenger properties reviewed below and its hypotensive effect, melatonin has been shown to centrally modulate autonomic nervous system (ANS) activity by inhibiting central sympatho-adreno-medullary (SAM) outflow and shifting autonomic balance in favour of vagal activity [141, 160-163]. In human and animal research, melatonin is shown to entrain disrupted autonomic rhythmicity and augment sympathoadrenal rhythm amplitude, reduce heart rate, norepinephrine levels, arousal and startle responsiveness, attenuate both orthostatic baroreflex and mental-stress-related sympathetic response and increase overall heart rate variability [140, 164-169]. As it is known that sympathetic activation of the paraventricular nucleus of the hypothalamus (PVN) inhibits melatonin secretion [5], restoring the autonomic imbalance seen is PTSD may also have reciprocal beneficial effects on the physiological melatonin secretion rhythm and as such further contribute to a reduction in PTSD symptoms.

Neuroimmunomodulation

The CS and immune system are bi-directionally connected through intricate interactions between the autonomic nervous system and GC hormones influencing the expression of circadian genes and cytokine signaling [29, 170-176]. Immune system reactivity follows circadian rhythms imposed by the SCN and sleep synchronisation, whereas chronodisruption is associated with altered immune function, disarranged immunity-related activity rhythms

and inflammation [170, 177-180]. Chronic stress with impaired GC hormone signaling and chronic dysregulation of the HPA axis and SAM system also enhances chronic inflammation, immunosuppression and immunosenescence and could herewith contribute to accelerated biological aging and stress-related pathology of inflammatory-related medical conditions [113, 181-183]. Growing evidence concordantly associates PTSD with peripheral immune dysregulation and low-grade inflammatory excess state (higher IL-6, IL-1b, C-RP, TNF-α and lower IFN-γ and IL-4 levels, lower lymphocyte counts, altered mononuclear and natural killer (NK) cell activity, etc.) [184-193], possibly involved in the overall increased morbidity rates seen in this disorder [194, 195]. Interestingly, low-grade inflammation even prior traumatic exposure has been also found to be a possible predisposing factor towards PTSD development [196].

Melatonin plays a fundamental role in the reciprocal relationship between the neuroendocrine and immune system [29, 170, 172, 173, 175, 176, 197-202]. Melatonin acts as an pluripotent immune regulator, immune-stimulating under basal or immunosuppressive conditions and immune-inhibiting in exacerbated immune responses [203]. It possesses numerous direct and indirect, as well as acute and chronic cellular and humoral immunomodulatory, antioxidative and anti-inflammatory properties both in vitro and in vivo [172, 200, 204-211]. Melatonin demonstrates endocrine, paracrine and autocrine effects in the leukocyte compartment, through modulation of pro-inflammatory enzymes, production of inflammatory mediators (i.e. cytokines, leukotrienes) and apoptotic processes [200, 211]. Melatonin also exerts important effects in cells of innate immunity [199]. Specifically, melatonin stimulates the production of granulocyte/macrophage progenitor cells, NK cells, CD4+ cells and various cytokines from NK cells and T-lymphocytes, while limits cell migration [202, 212]. In addition, animal models suggest that melatonin counteracts negative immune effects of acute stress [213]. For example, in animal models, melatonin inhibits the endotoxin-induced increase in serum TNF-α levels, improves humoral and cell-mediated immune responses in GC-induced immunosuppression and restores metabolic-stress-induced elevated IL-1β, IL-6, TNF-α, IFN-γ and CRP and reduced IL-4 and IL-10 levels [214-

217]. These properties suggest a central pleiotropic role of melatonin in physiological immune processes and immunosenescence and have placed melatonin among the newest promising agents in immunotherapy [211]. Of particular interest for cancer immunotherapy is the observation that melatonin causes synergistic effects with specific cytokines, which may lead to higher antitumoral activity and a lower incidence of side effects [204].

Metabolism

The CS is closely connected with the regulating expression and activity of key players in cellular metabolism [143, 218]. Chronodisruption can lead to pro-orexic lipid and glucose metabolic alterations and consequently to related pathological metabolic conditions (e.g., diabetes, obesity, metabolic syndrome) [219-221]. PTSD and PTSD-related endocrine findings have been repeatedly associated with higher rates of metabolic clinical manifestations such as higher BMI and obesity, higher leptin and insulin levels with lower insulin sensitivity, and higher risk for metabolic syndrome, type-2 diabetes and dyslipidemia (higher total cholesterol, triglycerides, low-density lipoprotein-cholesterol and lower high-density lipoprotein-cholesterol) [222-228].

Melatonin is a major metabolic regulator and responsible for an adequate energy balance and mobilization [229]. Among other functions, melatonin regulates glucose homeostasis and proper synthesis, secretion, and action of insulin, plasma lipid profile, activation of brown adipose tissue, and the browning process of white adipose tissue. [230-232]. In experimental animal models, M melatonin LT reduces both adiposity and body weight, inhibits insulin release, increases insulin sensitivity and ameliorates the altered biochemical metabolic alterations seen in animals fed on a high-fat diet (e.g., dyslipidemia, oxidative stress) [216, 233, 234]. Similarly, in clinical human research, melatonin treatment has been proven beneficial in patients with metabolic syndrome, diabetes and peri-/postmenopausal women resulting in normalization of lipid profiles and reduced HbA1c levels [235-237]. Melatonin seems also efficacious in the prevention of drug-related metabolic side-

effects (e.g., weight gain, abdominal obesity, hypertriglyceridemia), as for example observed in patients treated with olanzapine [238].

Oxidative stress and traumatic brain injury

Oxidative stress (OXS), defined as a disequilibrium between oxidant generation and antioxidant response, represents cellular chemical stress by an excess of free radicals (e.g., reactive oxygen species, ROS and reactive nitrogen species, RNS). OXS can be triggered by many exogenous (e.g., toxins, chemicals, UV-light, smoking) and endogenous (e.g., hyperglycemia, dyslipidemia, cytokines, chemokines) factors and deplete cellular defences, thus initiating inflammation [239, 240]. Free radicals from subcellular compartments lead to severe structural injuries and functional alterations of macromolecules, membranes, cellular organelles, as well as coding material (i.e. through lipid peroxidation or protein oxidation) [21, 239]. For example, telomere length decline, as a proxy for cellular aging, has been associated with OXS [241, 242].

OXS plays a major pathophysiological role in the development of many disorders, potentially including psychiatric and neurodegenerative conditions [239, 241]. The effects of early-life and traumatic stress on higher CNS and peripheral OXS-related marker levels have been investigated in animal models, but also clinical research. For example, early-life stress and PTSD have both been linked to shorter telomere length (a novel biomarker of accelerated cell aging and OXS) in clinical research [241, 243-245]. Respectively, higher levels of glutathione (a marker for neuronal OXS) were reported in dorsolateral prefrontal cortex and anterior cingulate cortex of PTSD patients using proton magnetic resonance spectroscopy [246]. These findings are supported by several animal PTSD-models reporting increased OXS markers and OXS-related metabolomic and transcriptomic effects in blood, adrenal gland, liver and CNS tissues compared to controls [246-248]. This line of evidence suggests that trauma-related stress, as seen in PTSD, potentiates OXS, thus modulating

neural integrity, accelerating cellular aging and increasing neuropsychiatric vulnerability [240, 249].

The is a large amount of data suggesting that melatonin exhibits distinct antioxidant characteristics and free radical scavenging properties, which has been also hypothesized to be the evolutional initial and primary function of melatonin [20, 250]. Given its small molecular size and its amphipathic behaviour, melatonin efficiently protects every subcellular compartment against OXS through a variety of mechanisms [21]. Melatonin and its metabolites exert direct scavenging effects on ROS/RNS and radical products, reduce free radical formation by support of mitochondrial electron flux, induce redox and other antioxidant enzymes while suppressing pro-oxidant enzymes, contribute to the maintenance of membrane stability, protect mitochondrial DNA and homeostasis, reduce metal-induced toxicity through concurrent chelating cascades and finally induce defence mechanisms suppressing inflammation [20, 21, 211, 239, 242, 250-258]. Especially in stress-related research, animal models have shown that melatonin can effectively counteract OXS and neurodegeneration, suppress various apoptotic markers and ameliorate the oxidant effects of GCs induced by stressful conditions [259-262].

These facts appear even more important, when considering the correlation between traumatic brain injury (TBI) and PTSD. The pathogenesis of TBI is directly related to secondary biochemical cascades following injury and exacerbating primary damage, which result in the imbalance between oxidant agents and antioxidant defence and, thus, lead to OXS, excitotoxicity, ionic imbalances, cerebral edema, neuroinflammation, neural dysfunction and cell loss with functional impairment [263-265]. Both PTSD and TBI commonly occur in the general population but are especially comorbid in military populations [266, 267]. TBI shares overlapping pathophysiological pathways with PTSD (i.e., altered brain networks with reduced prefrontal function, volume loss in amygdala, etc.), leading to similar symptoms (e.g., cognitive impairment, sleep disruption) [268, 269] higher levels of PTSD symptomology [267, 270-272] and increased vulnerability to the disorder [270, 273-275]. Prospective studies have confirmed TBI as a major predictor of PTSD risk [276]. In

animal models of TBI, but also in human RCTs, melatonin has proven beneficial in preventing and ameliorating the effects of the neurotrauma, such as OXS, brain edema, and neuronal degeneration, as well as TBI-related functional impairment through its antioxidant, neuroprotective and antiapoptotic qualities [277-282]. Interestingly, TBI in rats has been found to cause increased DNA methylation and reduced expression of the *Aanat* gene [283], encoding serotonin N-acetyltransferase, one of the two enzymes involved in the synthesis of melatonin from serotonin.

Cognitive function, memory and neurocircuitry

Both animal and human studies demonstrate cognitive performance being sensitive to the CS [284-286]. Cognitive performance as well as memory processing, formation and consolidation are directly influenced by the circadian clock, melatonin and the HPA axis [284-294]. Sleep promotes memory consolidation, particularly for emotionally salient information [285], while SD may reduce the connectivity between amygdala and PFC [295] and disrupt memory consolidation [296-300]. Accordingly, several studies have successfully replicated distinctive neuropsychological deficits (e.g. deficits in attention, learning & memory, executive function, decision making) in association to sleep disruption in humans [301-305].

Besides sleep disruption, acute and traumatic stress also affect neural correlates of memory formation [306-308]. PTSD is similarly associated with several cognitive deficits, crucial for the development and maintenance of the disorder [309-311] and in part directly related to sleep disturbances [312]. Specifically, impaired executive functioning, learning, cognitive information processing, free and cued recall, recognition and declarative memory performance, verbal memory, fear conditioning, fear extinction and explicit memory for emotional material have been repeatedly reported in patients with PTSD [311, 313-316]. Neuroimaging studies have reported hyporesponsive medial PFC regions, hyper-responsive amygdala and smaller hippocampal volume with decreased activation in patients with PTSD [310, 317-319]. These alterations are related to the impaired associations between contextual stimuli and aversive events, prediction errors during fear learning and extinction, disarranged regulation of negative emotion and fear gating by contextual information

reported in this disorder [320-323]. In addition, animal studies have put forth a significant impact of circadian rhythmicity on homeostasis, neurogenesis and neural activation in these exact brain regions [324-329].

Interestingly, research findings suggest a direct enhancing effect of melatonergic transmission in stimulus processing and memory consolidation, especially under stress [330-332]. In addition, in animal models melatonin has been associated with positive structural effects on synaptic plasticity and dendritic remodeling in cortical and hippocampal brain areas associated with cognitive and memory function, which may be caused by alterations in the regulation of cell adhesion molecules expression [93, 333]. Melatonin has also been shown to influence circadian clock gene expression in hippocampal neurons (see above) and to protect these neurons from oxidative stress, by preventing GC-related toxicity and inhibition of hippocampal neurogenesis and cell proliferation through decrease of receptor translocation to nuclei in models of SD and chronic stress [260, 334-336].

Melatonergic action has been shown to resemble sleep effects and prevent and/or reverse stress-, SD- and aging-related cognitive impairment and memory deterioration [334, 335, 337-340], as well as facilitate conditional cued fear extinction [341], without leading to next-day cognitive impairment, as seen with other hypnotics [342]. Reports suggest, that interventions aimed at restoring normal hippocampal function, disrupting dysfunctional aversive memories and enhancing extinction of conditional cued fear may serve future treatment strategies for PTSD [320, 341, 343].

Pain

Chronic pain syndromes and hyperalgesia to nociceptive stimuli are often reported in PTSD and are also associated with trauma history without PTSD [344-347]. Chronic pain is also considered a form of chronic stress and has been associated with hypocortisolism and enchanced HPA axis negative-feedback sensitivity, similar to PTSD [348-354]. Pain modulation and nociception exerts circadian variations [355-357] and interacts bidirectionally with sleep and the CS, with SD leading to hyperalgic states and acute or chronic pain to

sleep and chronodisruption [358-363]. In particular, pain modulation seems closely linked to melatonin, which acts direct or indirect through MT1, MT2, μ-opioid, $GABA_B$ and NMDA receptors at spinal and supraspinal levels [364-368]. The analgetic effect of melatonin is supported by both experimental and clinical evidence. Animal research has confirmed dose-dependent, antinociceptive and analgetic effects of melatonin in acute, chronic and inflammatory pain models [369-371]. In clinical human research, endogenous melatonin secretion has been shown to be responsive to acute pain episodes [372], while exogenous M melatonin LT has shown analgesic, antihyperalgesic and antiallodynic efficacy in intra- and postoperative analgesia [373] and experimental pain studies [374], as well as in some, but not all studies of chronic pain syndromes (e.g., fibromyalgia, irritable bowel syndrome, endometriosis, migraine, neuropathic pain) [366, 369, 375-378]. Melatonergic treatment could, thus, represent a novel efficacious alternative treatment in patients with chronic pain comorbidity, such as PTSD patients [366, 367, 369, 379].

Epigenetics

Epigenetic regulatory mechanisms at the chromatin, such as DNA (de-)methylation and histone modifications, act in concert bridging environmental and internal signals to modulate gene expression, thus resulting in transient as well as sustained transcriptional changes. Epigenetic modifications, as molecular consequences of stress and trauma experience, could play an important role in the aetiology of stress-related mental disorders and together with individual genetic predisposition explain disease susceptibility and stress resilience [380-383]. Early life events and childhood trauma are repeatedly shown to be associated with epigenetic changes and altered gene expression profiles especially in the CNS (e.g., hippocampus, amygdala), which influence stress responses and memory consolidation [382, 384-386]. For example, fear conditioning rodent models support the role of epigenetic regulation e.g. through stabilization of context- and cue-triggered fear conditioning [387, 388]. Moreover, subjecting rats to a an acute psychological stressful challenge has been shown to cause behavioral adaptations, which result from interactions between GR and the ERK1/2-

MSK1-Elk-1 signaling pathway leading to specific histone modifications in promoters of immediate early genes such as c-Fos and Egr-1 [389].

There is an increasing body of evidence in humans for gene programming and epigenetic regulation of specific genes in the pathophysiology of PTSD [388, 390-392]. Although there are no direct prospective findings on PTSD-specific epigenetic modifications, recent observations on the role of stress-related gene expression, early developmental influences and transgenerational effects are compatible with epigenetic explanations [393]. In particular, some GC-signaling related genes (e.g., GCR gene promoter 1F) are subject to stress- and trauma-related epigenetic regulation throughout life and may be useful as biomarkers associated with development, prognosis and symptom state of PTSD [394, 395].

The circadian machinery is highly involved in such epigenetic regulatory mechanisms, promoting specificity and seasonal/circadian plasticity of molecular environmental responses [396-398]. Epigenetic regulation utilizes to some extent highly sophisticated circadian transcriptional-translational feedback loops that modulate expression of cellular transcripts, while the circadian epigenome shares intimate links with chromatin remodelling (e.g., CLOCK protein has intrinsic histone acetyl transferase activity) [399].

Thereby, melatonin is particularly involved, modulating epigenetic processes in a circadian manner together with other epigenetic factors [239, 400-402]. Most importantly, melatonin is also suggested to exert direct beneficial effects in epigenetic regulation and protect from or even restore stress-related epigenetic changes [239, 401, 403-405]. In vitro, melatonin can regulate epigenetic modifications by both DNA methylation and histone modifications through its effects on nuclear receptors, co-regulators, histone acetylating enzymes and free radical scavenging [406-408]. Melatonin thus exerts prophylactic effects on the epigenome by decreasing gene-silencing related mRNA expression, inhibiting telomerase activity and significantly increasing chromatin remodeling (i.e. histone deacetylase isoforms, histone H3 acetylation activity) and gene transcription [406, 409].

Mood and anxiety

Depression and anxiety disorders are highly comorbid psychiatric conditions in PTSD patients, which may share common risk factors and pathophysiological background [410, 411]. Most human research findings focus on the role of CS in depression, proposing that SD and chronodisruption are under-recognized but vital underlying mechanisms contributing to the development of mood disorders [412-415]. Several studies suggest, for example, an important role of circadian gene expression and polymorphisms in modulating reward motivation and active behaviour and, thus, determining mood disorders' susceptibility, recurrence and treatment response [413, 414, 416, 417]. A plethora of findings has also reported significant and acute negative effects on positive mood correlates in the aftermath of SD conditions in healthy people [418, 419]. Interestingly, studies in rats have shown that SD impacts on hippocampal serotonin and free GC hormone levels [420]. With respect to anxiety and anxiety disorders, evidence from human research has primarily focused on the relation between these conditions and SD [421, 422], while only relatively few studies examined circadian gene-related effects on anxiety-related behaviour [423, 424].

Although interventions able to resynchronize the human circadian system (i.e. SD, light therapy, etc.) have shown some potential in the treatment of depression [425, 426], there are no data unquestionably supporting the antidepressant efficacy of melatonin and melatonin receptor agonists [75, 427, 428], with the exception of agomelatine - a MT1/MT2 agonist and 5-HT_{2C} antagonist with antidepressant and anxiolytic potency [72, 429-432]. On the other hand, there is some evidence for (mostly acute) anxiolytic effects of melatonin and melatonin receptor agonists [431, 433]. Nevertheless, besides one single case-report on agomelatine treatment in PTSD, there is no clinical evidence for melatonin and melatonin receptor agonist effects in PTSD.

Further Co-morbidities

Traumatic experience and PTSD are frequently related to several specific co-morbidities, such as chronic fatigue syndrome (CFS) [434-437], fibromyalgia [438-442], rheumatoid arthritis [443]. These syndromes share a very similar underlying neuroendocrinological profile

to PTSD (e.g., hypocortisolism, blunted diurnal cortisol rhythm and HPA axis reactivity) [444-449] and have all been repeatedly associated with evidence supporting circadian disruption [354, 450-459]. Interestingly, there is also relatively well-founded evidence for the efficacy of an adjuvant melatonergic treatment in these disorders. Several RCTs and open trials reported efficacy of melatonergic treatment with respect to the reduction of pain perception and sleep in fibromyalgia, as well as fatigue, concentration, motivation and activity in CFS, although there is only a small number of studies in general [377, 379, 460-465].

Similarly, traumatic stress experience and PTSD have been associated to an overall higher risk of cancer incidence, recurrence and mortality, partly in a dose-response manner [194, 195, 466-469]. Cancer biology has been intensively linked to the CS and chronodisruption [470-472], while melatonin has shown promising qualities as an oncostatic and adjuvant cancer treatment as there is evidence that melatonin can promote endocrine re-synchronization, tumor growth regression, stability of disease without tumor progression, as well as survival in cancer patients [473-477]. Melatonin reduces severe ROS and RNS-related DNA damage inducing cancer initiation and tumor progression [5, 6], controls tumor growth by activating signal transduction pathways, altering the expression of growth and differentiation-related genes [409, 478]. Melatonin is shown to upregulate the tumor suppressor gene GPC3, inhibit telomerase activity and endothelin-1 synthesis, inhibit COX-2 and p300 and downregulate cancer-related oncogenes (i.e. breast cancer EGR3 and POU4F2/Brn-3b) either by methylation of the Aromatase gene (CYP19) or deacetylation of CYP19 histones resulting in chromatin closing and binding inhibition of transcriptional factor triggering the expression of oncogenes [404, 409, 478-480]. A recent meta-analysis of RCTs confirmed the efficacy and safety of melatonin in cancer treatment [474], suggesting that melatonin is influential in inhibiting both cancer initiation and cancer cell growth.

Discussion

Loss of circadian rhythmicity fundamentally affects the neuroendocrine, immune and autonomic system, similar to chronic stress and may play a central role in the development of

stress-related disorders. Disruption of sleep and of circadian rhythm after trauma represent core rather than secondary features of PTSD [37-40, 62, 63, 481] and are both a precipitating and perpetuating factor of the disorder [482-484]. Recent articles have focused on the role of the sleep and circadian disruption in the pathophysiology of posttraumatic stress disorder (PTSD), suggesting that chronodisruption plays a causal role in PTSD development. Circadian disruption could precipitate the neurobiological correlates of the disorder through impaired homeostatic balance with neuroendocrine, immune, metabolic and autonomic dysregulation, resulting in the extensive symptomatology and co-morbidiy of PTSD [41, 151-155, 184, 443, 485-495].

Standard sleep pharmacotherapies in PTSD may treat sleep quantity sufficiently, but often fail to improve daytime functioning and restore the unique CS-related neurobiological changes in PTSD [6, 496]. Thus, the development of pharmacological interventions that would counteract changes in PTSD-related neurocircuitry and restore CS-related alterations could represent an interesting novel therapeutic strategy [413, 497-499]. Such pharmacotherapies could be incorporated into any standard PTSD treatment and be applied in addition to psychological-behavioral interventions, in cooperation with sleep specialists [61].

Melatonin is fundamental for circadian regulation and also plays a crucial role in several brain processes affected in PTSD. Recent experimental findings emphasize on the role of melatonin in mechanisms of sleep, cognition and memory, metabolism, pain, neuroimmunomodulation, stress endocrinology and physiology, circadian gene expression, oxidative stress and epigenetics. The efficacy of melatonin and melatonergic treatment beyond sleep regulation has been considered and investigated in numerous clinical conditions also found as comorbidities in PTSD, while most results confirm the very low toxicity and side-effects range of melatonin over a wide range of doses [78, 460, 500]. The hypnotic, rhythm resynchronizing, antioxidant, anti-inflammatory, antinociceptive, neuroprotective, pro-cognitive, metabolic, antiapoptotic and anxiolytic actions of melatonin and melatonergic agents could therefore represent a promising adjuvant contribution to the

clinical treatment and prevention of stress-related syndromes and comorbidities in mental disorders in general and PTSD in particular [10, 41, 499, 501-503] (*cf*. Figure 3).

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Conclusions

Understanding the mechanisms susceptible to chronodisruption following trauma exposure and their role in a chronically dysregulated circadian network in PTSD could be valuable towards enabling innovative preventive strategies and psychochronobiological treatment possibilities in PTSD patients and high-risk trauma-exposed populations [8, 39, 58, 104, 504]. Unfortunately, relevant clinical literature is relatively sparse and regularly neglecting the potential effect of CS on the development of the pathophysiological findings in this disorder [57, 58, 114, 505]. Adjuvant melatonergic treatment could provide a potentially promising treatment strategy with beneficial effects in the treatment of PTSD and especially PTSD-related syndromes and comorbidities. This theoretical concept deserves thorough further investigation through pre-clinical research and clinical confirmation through RCTs assessing the efficacy of melatonin and melatonergic treatment in the prevention and treatment of PTSD.

List of abbreviations

ACTH	Adrenocorticotropic Hormone
ANS	Autonomic Nervous System
CAR	Cortisol Awakening Response
CRH	Corticotropin-Releasing hormone
CS	Circadian System
CSF	Cerebrospinal Fluid
GC	Glucocorticoids
GR	Glucocorticoid Receptor
HPA axis	Hypothalamic-Pituitary-Adrenal axis
ipRGC	Intrinsically Photosensitive Retinal Ganglion Cells
MT_1	G-protein-coupled Melatonin Membrane Receptor 1
MT_2	G-protein-coupled Melatonin Membrane Receptor 2
NK cells	Natural Killer Cells
OXS	Oxidative Stress
PGL	Pineal Gland
PTSD	Posttraumatic Stress Disorder
PVN	Paraventricular Nucleus of the Hypothalamus
RZR	Receptor-related Z Receptor
RCT	Randomized Controlled Trial
REM	Rapid-Eye-Movement
RNS	Reactive Nitrogen Species
ROR	Receptor-related Orphan Receptor

RORA	Retinoid-related Orphan Receptor Alpha
ROS	Reactive Oxygen Species
SAM system	Sympatho-Adreno-Medullary System
SCN	Suprachiasmatic Nucleus
SD	Sleep Deprivation
SNRI	Serotonin-Norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
TBI	Traumatic Brain Injury

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Author Contributions

AA conceptualized the paper, managed the literature searches and wrote the first draft of the paper. ACEL revised the draft and discussed the presented concepts with AA. Both authors have contributed to, read and approved the final version of the manuscript.

Conflicts of Interest

AA and ACEL report no biomedical financial interests or potential conflicts of interest and none of the authors received funding for this article.

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Figures

Figure 1. Simplified diagram of pathways modulating melatonin secretion and melatonergic effects.

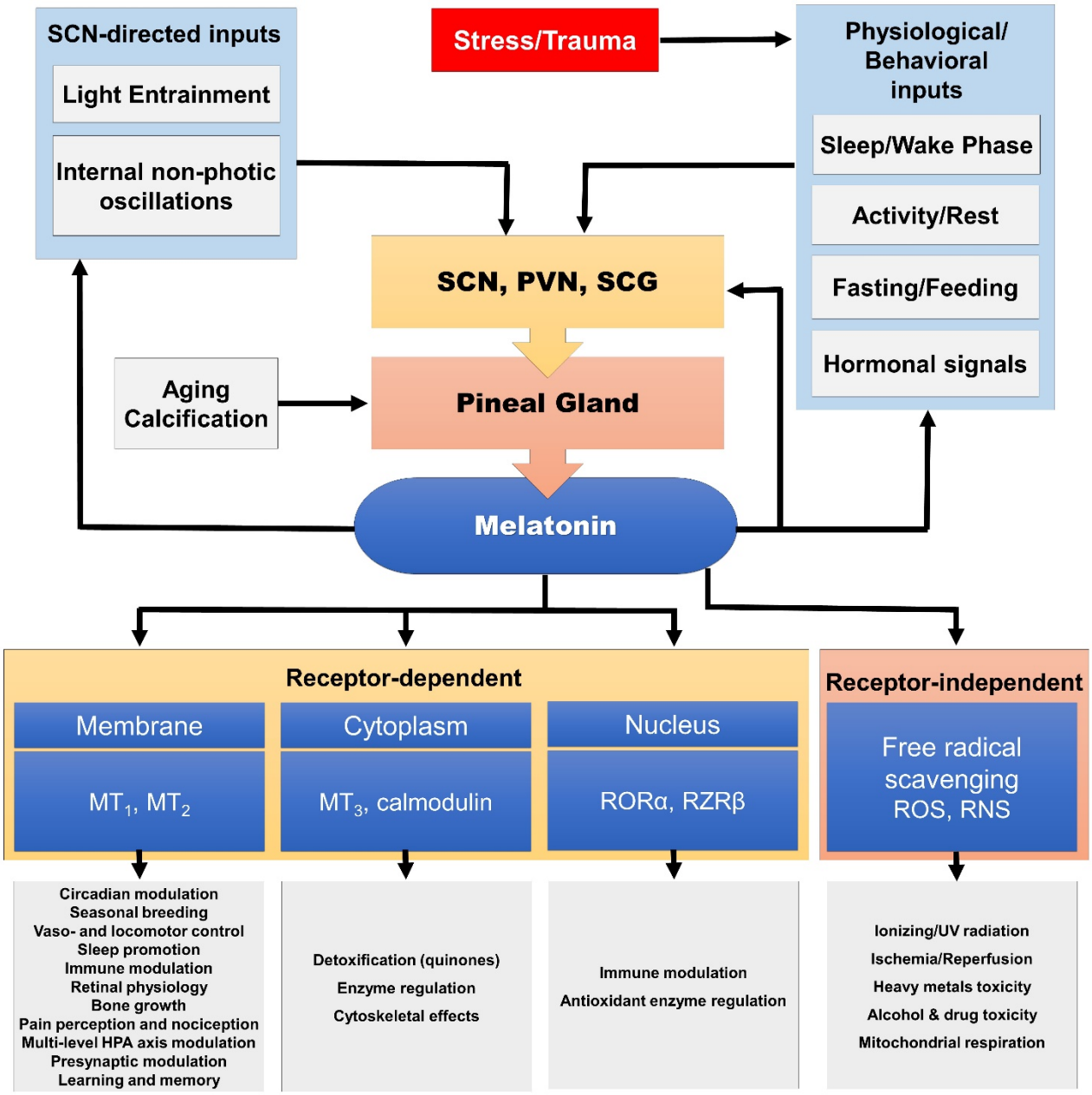

Figure Legend:

SCN: suprachiasmatic nucleus; PVN: paraventricular nucleus; SCG: superior cervical ganglion; MT1, MT2: melatonin membrane receptors 1 and 2, MT3: quinone-reductase-II; ROR: retinoid orphan nuclear receptors; RZR: retinoid Z nuclear receptors; ROS: reactive oxygen species; RNS: reactive nitrogen species; HPA axis: Hypothalamus-pituitary-adrenal axis. Modified from [10, 18, 25].

Figure 2. Proposed model of PTSD development: From trauma to sustained chronodisruption.

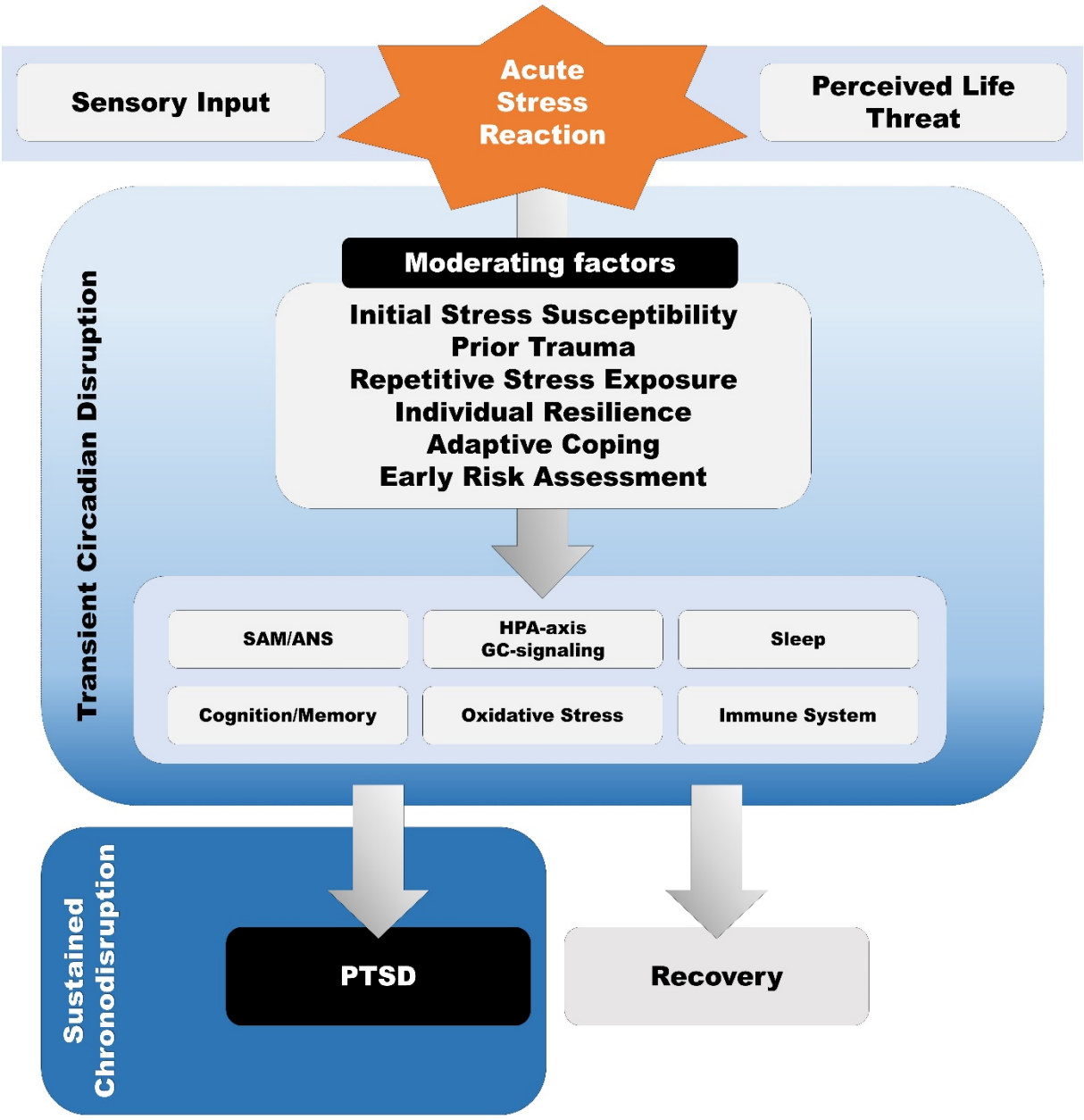

Figure Legend:

Proposed model of PTSD development. Arrows: temporal order; SAM: sympathoadrenal-medullary system; ANS: autonomic nervous system; HPA-axis: hypothalamus-pituitary-adrenal-axis; GC: glucocorticoid.

Figure 3. Overview of beneficial melatonergic effects on PTSD-related biological correlates

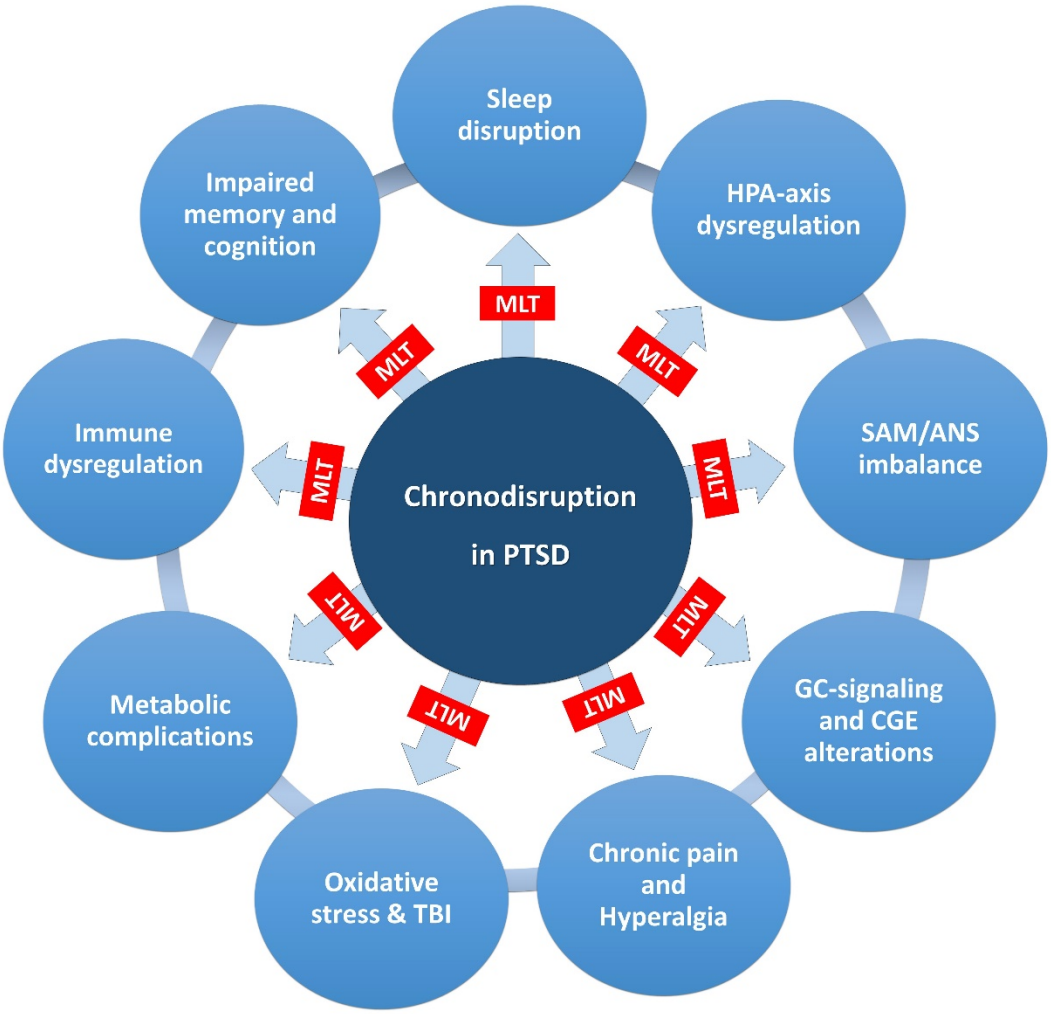

Figure Legend:

Melatonin exerts preventing and restoring/synchronizing effects with beneficial actions on the main PTSD-related biological alterations (red boxes). MLT: melatonin; HPA-axis: hypothalamus-pituitary-adrenal-axis; SAM: sympathoadrenal-medullary system; ANS: autonomic nervous system; GC: glucocorticoid; CGE: circadian gene expression; TBI: traumatic brain injury.